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EXPERIMENTAL VACCINE SHOCK AND THE RESISTANCE TO TUBERCULOSIS

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Recently Baldwin and L'Esperance[1] described observations concerning the effect of intravenous vaccine injections (protein shock) on tuberculous guinea-pigs, and particularly the unusual alteration in the tissue reaction to the tuberculous process from that commonly observed in these animals. One of us,[2] dealing with the relation of the serum ferments and antiferment to tuberculosis, has suggested the possibility that the observations of Baldwin and L'Esperance might be due to the increase in the antiferment titer of the treated animals, which would tend to protect the tubercle from digestion by the strongly active proteolytic serum ferments, and thereby prevent the rapid dissemination of the infecting bacilli from the foci.

English observers early noted and suggested the clinical use of the increase in the antiferment titer following ordinary vaccine injections, and Bruce[3] described the increase in the weight curves of patients who were under vaccine treatment for a considerable period of time, a fact that Mircoli[4] has demonstrated experimentally in normal animals following tuberculin injections.

Inasmuch as any intoxication ordinarily results in an almost immediate increase in the excretion of nitrogen, it is evident that the increased weight the various authors have noted following vaccine injections must involve the bringing into play of some compensatory mechanism, through the action of which the organism is able to retain a greater amount of nitrogen than before the vaccine shock. There is considerable evidence that the increase in the antiferment is one of the factors involved in this mechanism,[5] particularly in the smaller animals in which the serum is rich in proteolytic ferments.

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[1] Jour. Immun., 1917, 11 p. 283.

[2] Petersen, W. F.: Arch. Int. Med., 1917, 20, p. 716.

[3] Brit. Med. Jour., 1910, 1, p. 430.

[4] Pathologica, 1914, 5, p. 118.

[5] Jobling, J. W., and Petersen, W. F.: Ztschr. f. Immunitätsforsch., 1915, 24, p. 219.

In the following experiment we have followed the weight curves, the nitrogen excretion, as well as the serum alterations of animals (rabbits, 4 in the series) which were twice given intravenous doses of a colon vaccine. The animals, of approximately the same age and weight, were given the 1st injection of 20 million killed colon bacilli on the 8th day at 10 a. m., serum being taken from the ear vein before the injection, 6 hours after and on the following day. A temperature reaction of approximately 3.5 C. followed the injection. A second injection was made on the 30th day of the experiment; this time only 10 million organisms were used, serum being taken before and 2 days after the injection. Following this injection the temperature reaction was slightly over 1° C.

In Chart 1 the curves illustrate the averages for all the animals, the solid line representing the vaccine animals, while the dotted line represents the curve of the normal animals.

It will be observed that the weight curve of the vaccine animals decreased slightly after the 1st injection, remaining below that of the controls for the entire period to the time of the 2nd injection. After this the vaccine animals continued to gain slightly over the controls until at the close of the experiment the vaccine animals weighed approximately 140 gm. more than the controls.

The nitrogen excretion, as determined by the Kjeldahl method, indicated a total excretion of 18.4 gm. for the vaccine animals as compared with 15.2 gm. for the controls. The increase in nitrogen excretion apparent in the curve during the latter part of the experiment was due to a greatly increased food ration given the animals during the latter half of the experiment.

When these findings are correlated with the changes in the proteolytic balance of the serum we find that the vaccine animals responded to the vaccine shock with a considerable augmentation of the antiferment, which, even after 3 weeks, was still at a higher level than at the beginning of the experiment, and was increased after the 2nd shock, from 35 to 47%. The curves for the normal animals also showed some increase during the course of the experiment, but this spontaneous change was much less than that following the vaccine injection.

In determining the proteolytic titer of the serum we have used a method suggested by Flatow,[6] that is, the incubation of casein solution with the serum for a definite time. The digestion that results is the index of the relative proteolytic balance existing between the proteolytic ferments present (protease and ereptase) and the antiferment. It is not to be regarded as the index of the total amount of protease which

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[6] München. med. Wchnschr., 1914, 61, p. 1500.

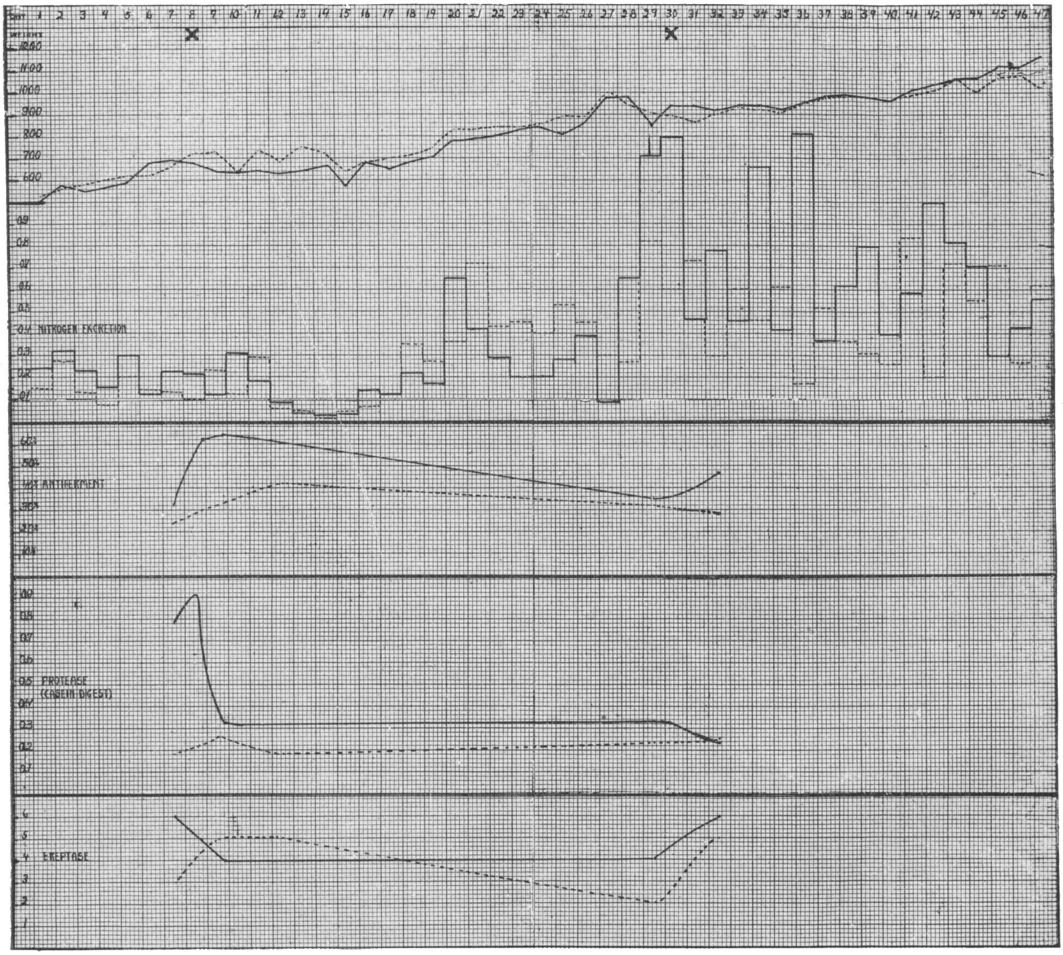

Chart 1.—Effect of vaccine shock (injections indicated by X) on the weight, nitrogen excretion, antiferment, proteolytic index and ereptase titer of rabbits. The curves illustrate the averages for all the animals. The solid line records the results secured in the experiments with the vaccine animals and the dotted line shows the curve obtained with the control animals.

is brought into effect only when the antiferment is removed by some means, either through the acidification of the serum or the removal of the antiferment by the lipoid solvents. In making this determination we have used 0.5 c.c. of serum and incubated for 48 hours with 2 c.c. of a 1% solution of neutral casein. The coagulable proteins were then removed and the noncoagulable nitrogen determined by the Folin method.

The differences between the boiled control and the tube which had been incubated at 47 C. have been charted in terms of 10th mg. It will be observed in the chart that after a short rise immediately following the vaccine injection, the proteolytic index of the serum was markedly diminished from the originally rather high titer, and the decrease was continued after the 2nd vaccine injection as well. The control animals showed very little alteration during the course of the experiment.

The short rise apparent immediately after the vaccine injection is due to the marked mobilization of protease which takes place following shock of this kind.[7] When this has disappeared, the effect of the increase in the antiferment becomes evident and depresses the proteolytic titer to a point far below the original titer prevalent before the vaccine shock.

The ereptase titer illustrated in the last curve of the series showed no characteristic alteration, although it too was decreased in the vaccine animals, while the control animals showed a slight increase in the titer.

DISCUSSION

An analysis of the serum alterations that take place following vaccine shock in these animals would indicate that one of the fundamental changes effected had to do with the decrease in the proteolytic index that results from the increase in the antiferment. With this observation as a basis we can understand that, despite the increased nitrogen elimination incident to shock, the animal tends to retain nitrogen to a greater degree than before the vaccine shock, so that such animals actually show a net gain in weight after the first effects of the shock have worn off.

It is from the standpoint of the resistance of the organism to tuberculosis, however, that we believe these alterations to be of greater interest. The progress of tuberculous infection in the guinea-pig and the rabbit is one of relatively great rapidity, the protecting tissue reaction which, in man, very probably forms the great bulwark against the progress of the disease, is largely lacking; indeed, fibrosis about the foci that might be comparable to the condition in man is rarely met with. We must keep in mind that these animals differ from man in the relatively great concentration of proteolytic ferments in the serum which are balanced by a narrow margin of antiferment, a condition the exact reverse of that found in man. In the smaller animals any tendency toward fibrosis is apt to be encountered by the digestive effect of the serum, and it is only when the antiferment is increased that a greater development of fibrous tissue is noted, as has been described by Baldwin and L'Esperance. This relation of the antiferment (and of the lipases) to the resistance of tuberculosis has recently been emphasized by Fernandez[8] in an interesting paper.

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[7] Jobling, J. W., and Petersen, W. F.: Jour. Exper. Med., 1915, 21, p. 239.

In view of the considerable differences in the proteolytic activity of the serum of the smaller experimental animals and man, it might seem warranted to observe considerable caution in the interpretation of experiments relating to tuberculous resistance in these animals unless proper recognition of the difference is kept in mind.

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[8] Siglo méd., 1917, 64, p. 376; abstr. in Jour. Am. Med. Assn., 1917, 69, p. 159.